49. The method according to claim 22, wherein intestinal extracts are administered for the prophylaxis and treatment of Crohn's disease.

50. The method according to claim 22, wherein intestinal extracts are administered for the prophylaxis and treatment of colitis ulcerosa.

51. The method according to claim 22, wherein allergy-specific allergens are administered for the prophylaxis and treatment of allergies. --

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Remarks

Reconsideration of this application in light of the following remarks is requested.

Claims 15-51 have been added.

Claims 6-14 have been cancelled, and thus, the rejections of claims 6-14 are moot. However Applicant notes that the claims were rejected under §112, and also §103 over GB 2,312,165 to Lyons ("Lyons") in view of U.S. Patent No. 6,174,529 to Michael ("Michael").

Enablement

Applicant acknowledges the Examiner's concern over an exhaustive search (page 3 of the Office Action). However, the present invention does not claim special combinations of autoantigens and allergens and special bisphosphonates, but a generally applicable method for the treatment of autoimmune diseases and allergies.

The basis of the application is the discovery that bisphosphonates are able to stimulate gamma/delta-T-cells. The stimulated gamma/delta-T-cells inactivate those cells of the immune systems (gamma/delta-T-cells, B-cells), which recognize the co-applied allergen and autoantigen. Thus, the reaction of the immune system to the respective allergen or autoantigen is reduced or inhibited respectively.

Contrary to the Examiner's assertion that "it would be unreasonable to expect the many diseases or conditions ... to respond to the [previously claimed] method" (Office action page 2), it is

precisely because the medicament is directed to the immune system that the invention is applicable to all thinkable autoantigens and allergens.

In any specific individual, diagnosis of an allergy often requires a battery of extensive allergy tests for finding out to which allergen the patient is sensitive. However, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). *See* MPEP 2164. The Examiner is respectfully reminded that "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*,858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 50204, 190 USPQ 214, 21719 (CCPA 1976)). *See* MPEP 2164.06.

After the allergen has been identified, the patient is treated by combination of the respective autoantigen or allergen and a bisphosphonate.

Test results

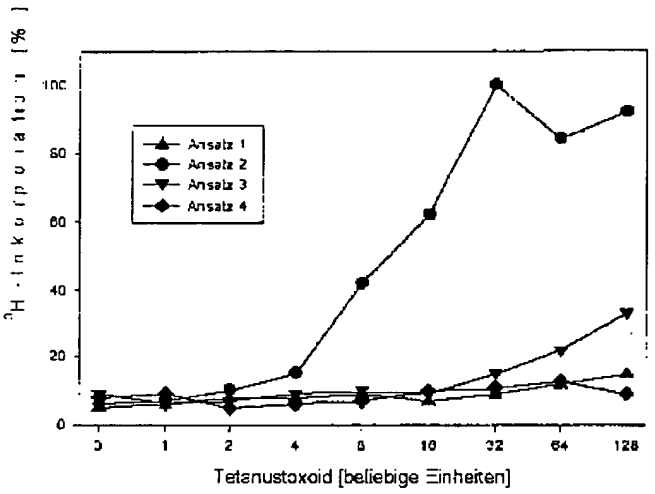
The following results were supplied by the inventor, and an affidavit or declaration may be supplied at the Examiner's request.

The inactivation of antigen specific immune cells by bisphosphonates stimulating gamma/delta-T-cell has been shown by ex vivo-experiments. In the beginning of the test, tetanus toxoid was injected *i.m.* to voluntary test persons who had already been immunized against tetanus. Fourteen days after this boostering, blood was taken from the test persons. PBMCs were obtained from the blood and taken in culture. To four culture samples, tetanus toxoid and alendronate were added according to the following scheme:

1. PBMC
2. PBMC + tetanus toxoid
3. PBMC + alendronate
4. PBMC + tetanus toxoid + alendronate

Subsequently, the proliferation of the cells for all samples was measured as a reaction of the incubation with tetanus toxoid by 3H-Thymidin-incorporation.

As expected, in control 1 the rate of proliferation as a response to tetanus toxin was low. The highest rate of proliferation was



Y: ^{3}H-incorporation

X: tetanus toxoid (optional units)

measured in sample 2, because in the preliminary culture (in presence of tetanus toxin), specific reactive clones were raised. In sample 3, only a low increase of the rate of proliferation was measured.

The rate of proliferation in sample 4 was very low. This result is based on the fact that gamma/delta-T-cells activated by alendronate inhibit the proliferation of the tetanus toxoid specific immune cells. Analogous experiments have been made by using the bisphosphonates pamidronate and ibandronate. These experiments had similar results.

Cited art

Lyons is limited to using ibandronate (a bisphosphonic acid) for a symptomatic treatment of inflammations and articular diseases in rheumatic form, which can be a side effect of autoimmune diseases, not treatment of the autoimmune disease itself.

In contrast, the present invention relates to bisphosphonates which are suitable for the treatments of autoimmune diseases themselves.

Michael is limited to teaching the use of therapeutic protein. Moreover, the uncertain action of the administration of autoantigens and allergens by themselves with the treatment of autoimmune diseases is proved by the results of the clinical studies (*see* http://www.autoimmuneinc.com/clinic.myloral.html). For example, AutoImmune Inc. had to stop a clinical study phase III recently, because an inexplicable large placebo effect has been found, which gives rise to doubts to the action of the substances.

MPEP §2143.02 states that prior art can be combined only where there is a reasonable chance of success:

> *Obviousness does not require absolute predictability, however, at least some degree of predictability is required.*

Likewise, Section 2142 of the MPEP provides:

> *...the examiner must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made.....The examiner must put aside knowledge of the applicant's disclosure, refrain from using hindsight, and consider the subject matter claimed 'as a whole'.*

Here, neither Lyons nor Michael teaches, or even suggests, the desirability of the combination. Lyons teaches treating inflammation, and thus cannot be combined with Michael. Thus, it is clear that neither patent provides any incentive or motivation supporting the desirability of the combination. Therefore, there is simply no basis in the art for combining the references to support a 35 U.S.C. §103 rejection.

In this context, the MPEP further provides at §2143.01:

> *The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.*

In the above context, the courts have repeatedly held that obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination.

In the present case it is clear that the Examiner's combination arises solely from hindsight based on the invention without any showing, suggestion, incentive or motivation in either reference for the combination as applied to the claims.

Should the Examiner have any questions or comments, the Examiner is invited to telephone the undersigned at the number listed below.

Respectfully submitted,

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Date: Jan. 4, 2002

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